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**Title page:**

**Temporomandibular disorders in head and neck cancers: overview of specific mechanisms and management.**

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**Abstract:**

Diagnosis classification system of Temporomandibular disorders (TMD) is based on the biopsychosocial model of pain. The pathogenesis is poorly understood, leading to difficulties in treating these multifactorial conditions. The predisposing factors are pathophysiological, psychological or structural processes that alter the masticatory system and lead to an increase in the risk of development of TMD.

The purpose of this integrative review was then to point out the specific mechanisms of TMD in the oral oncologic context to optimize the TMJ functional results in the management of patients with oral oncologic conditions.

We explored in this paper the role of Axis II assessment of the biopsychosocial model of pain, the involvement of mechanical concepts such as dental occlusion, mandibular condyle positioning and related-structures reconstruction, and the stomatognathic changes induced by radiation.

**Text:**

***Introduction:***

Temporomandibular disorders (TMD) are a significant public health problem affecting approximately 5% to 12% of the general population [1]. It can be defined as a group of heterogeneous musculoskeletal disorders, characterized by regional pain in the preauricular areas or facial area or by limitation or interference in jaw movement. Subtypes of TMD include pain-related disorders, such as myofascial pain and arthralgia, and disorders associated with the temporomandibular joints (TMJ), such as internal derangements and degenerative joint disease [2]. These common musculoskeletal conditions result in pain and disability [3], impacting the patient's daily activities [4], its psychosocial functioning [5,6], and its quality of life [1,7].

Therefore, the TMD diagnosis classification system is based on the biopsychosocial model of pain that includes an Axis I physical assessment using reliable and well-operationalized diagnostic criteria and an Axis II assessment of psychosocial status and pain-related disability [1]. Nevertheless, the pathogenesis is poorly understood, leading to difficulties in treating these multifactorial conditions. Understanding the possible etiologies of TMD is then extremely important in identifying and avoiding potential pathologic factors [8,9]. Predisposing factors are pathophysiological, psychological or structural processes that alter the masticatory system and lead to an increase in the risk of development of TMD. The set of epidemiological, psychological, biological, occlusal, mechanical factors or traumatic factors should affect differently the TMJ in oncologic and in general population.

In head and neck oncologic context and particularly in cancers affecting the mandible directly or indirectly, the mechanisms leading to TMD are complex and involve elements affecting the general population and some additional specific outcomes due to oncologic condition or specific treatments. The purpose of this integrative review was then to highlight the specific mechanisms of TMD in the oral oncologic context to optimize the TMJ functional results in the management of patients with oral oncologic conditions.

## **Materials & Method:**

This overview followed the methodology below. Aim of article selection was to respond to three pathophysiologic axis of TMD onset in the oral oncologic context: the role of biopsychosocial model of pain, the mechanical paradigm including dental occlusion, mandibular condyle positioning and related-structures reconstruction, and finally the stomatognathic system changes induced by radiation.

The search of publications included the MEDLINE, the Cochrane library, clinicaltrials.gov, and WHO International Clinical Trials Registry Platform databases. The terms searched in each database depended on the pathophysiologic axis explored. Terms searched were “Temporomandibular Joint Disorders and Neoplasms”, “Temporomandibular Joint Disorders and Cancers”, “Temporomandibular Joint Disorders and Psychological Distress”, “Neoplasms and Psychological Distress”, “Cancers and Psychological Distress”, “Temporomandibular Joint Disorders and Mandibular Reconstruction”, “Temporomandibular Joint Disorders and Radiotherapy” and “Pain and Mouth Neoplasms”. There were no limits in the search (even in publication dates), which ended the twenty-first of August 2019.

Studies were first screened based on a combination of their title and their abstract with double reviewing (RN and MS). Full paper was then reviewed and was considered if it responded to one of the three axis of interest.

## **Results:**

### *Axis II assessment of the biopsychosocial model of pain*

There is a considerable evidence that psychological and psychosocial factors influence TMD, leading to the concept of biopsychosocial model of pain [1,5,6,9]. Both assessment of psychosocial status and pain-related disability are included in axis II assessment of the biopsychosocial model of pain used in the TMD diagnosis system [1]. More precisely, many parameters are involved in axis II, within a core patient assessment instrument set, such as assessment of pain intensity, pain disability, jaw functioning, psychosocial distress, parafunctional behaviors, and widespread pain.

It is currently known that several premorbid psychological variables predict first-onset TMD, including reported somatic symptoms, psychosocial stress, and affective distress. Measures of somatic symptoms seem to be the most strongly associated variables with TMD onset, but perceived stress, previous life events, and negative affect also the predicted TMD incidence [6]. It is likely that all these elements are highly increased in head and neck cancer patients, due to their disease status itself but also given the curative or palliative treatments to undergo or to be planned [10–18]. The management of these serious conditions can in particular involve surgery, radiation therapy, and sometimes chemotherapy. Surgical treatments are aggressive and can severely impact a survivor's quality of life through disfigurement and functional disabilities [10,11,15,18–22]. Impaired emotional and physical functions appear to be associated with persistent psychological distress (e.g., depression and anxiety) in these patients [18,23–25]. Given that psychological status is a major element of axis II of the TMD classification system, it is likely that an oncological context increases the risk of TMD by raising psychosocial comorbidities. To solve this

problem, psychological interventions focused on relaxation, cognition, or behavior should be used in preventing such persistent psychological distresses [21,23,24,26]. On the other hand, up to 80% of these patients have persistent-pain due to the spread of the primary tumor, because of the consequences of surgery, or by developing oral mucositis or neuropathy as a toxic side effect of radiotherapy, chemotherapy or both [27,28]. Pain can present as nociceptive pain, neuropathic pain or both, myofascial pain or other mixed types [27,29–31]. The pain score deterioration is generally observed during the first 3 months after head and neck cancers surgical treatments, followed by a slow recovery. While surgery is responsible of various onset of persistent-pain, radiation treatments or chemotherapy also increase pain-related symptoms [28]. Radiotherapy can produce acute and chronic side effects, such as neuropathic pain or oral mucositis, with a potential impact on patient's compliance to therapy, quality of life and clinical outcomes [32]. The quality of life is worse with chemoradiotherapy compared with radiotherapy alone [33]. Painful peripheral neuropathy is on the other hand, well described with the use of vincristine, platinum, taxanes and other agents [28]. Persistent-pain appears to be a major criterion contributing to the deterioration of the quality of life after both surgical and medical treatments. Persistent-pain is moreover associated with major depression in cancer survivor, decreasing the quality of life [34,35]. Finally, pain-related disability consists in another major element of axis II encountered in oncological context, increasing the risk of TMD. It can be highlighted the importance of providing a combination of pain medications, physical therapy, exercise, psychosocial intervention, and alternative therapies in the management of pain-related disability, and also to prevent the occurrence of TMD. A multidisciplinary pain clinic for patients with complex pain issues requiring specific analgic treatments

should also be considered [27,28,34]. There is an overall insufficient evidence from randomized clinical trials to suggest an optimal pharmacological intervention for head and neck cancer pain post-treatment [36]. Head and neck cancer pain, on the other hand, poorly responsive to opiates, and head and neck cancer patients quickly develop opiate tolerance [28–30,36], partly due to genetic variation of the mu-opioid receptor gene (*OPRM1*) [37]. Nevertheless, recent non-randomized studies showed effectiveness of gabapentin in improving the pain control in patients with neuropathic cancer pain, already treated with opiates [38].

Others elements of axis II could be implied in pathogenesis of TMD in head and neck cancer patients. There is also a high prevalence of poor sleep quality in long-term head and neck cancer survivors. Extensive neck dissection, poor mental health, and psychological disability are contributing factors to poor sleep quality [39]. There are currently no data relating to prevalence of parafunctional behaviors, such as bruxism, in these patients, which are known contributing factors to TMD. However, bruxism and dysfunctional oral habits were shown to be risk factors for the presence of TMD symptoms after mandibular surgical treatment of patients cancers-free [40]. Searching and treating such habits before and after oncological treatments should help prevent TMD. On the other hand, daily smoking and increased frequency of alcohol consumption are both associated with TMD symptoms [41]. Given the high prevalence of these two cocarcinogens in patients with cancer of the oral cavity, it is likely that they increase the risk of developing TMD in this population. Addictions cessation is essential for oncological reasons, but participate also in the prevention of TMD.

*Mechanical paradigm: role of dental occlusion, mandibular condyle positioning and related-structures reconstruction*

Of the treatments used, surgery is the cornerstone in many cases, which sometimes leads to tooth loss, broken mandibular continuity or, in contrast, mandibular reconstruction.

Jaw anatomy and function are particularly complex, and reconstructing the jaw is a surgical challenge. Masticatory function needs a well coordination of many structures, such as masticatory muscles or temporomandibular joints, which all function symmetrically with the opposite side of the face [42]. While variable degrees of articular disc displacement are possible after paramedian split mandibulotomy [43], jaw movements and chewing function typically deteriorate after a segmental mandibulectomy or hemimandibulectomy [19,44]. Mandibular reconstruction of a segmental resection has positive effects on mandibular function, increasing mandibular kinematics and maximum voluntary bite force [45]. Aims of mandibular reconstruction are thereby to restore the mandibular shape, to contain the intraoral elements and mainly to preserve the masticatory function [19]. When a bone free flap reconstruction is performed after segmental mandibulectomy, the anatomical position of the TMJ must be considered to preserve its function, to obtain adequate mandibular mobility and effective mastication, to limit trismus or avoid the TMJ malposition responsible for TMJ pain, internal disorders of the TMJ, or malocclusion [44,46]. Artisanal reconstruction may, however, lead to inadequate size, placement or conformation of the bone flap, thereby inducing TMJ biomechanical abnormalities and the associated dysfunctions thereof [47–49]. Indeed, mandibular condyle position affects dental occlusion. It can be surgically misplaced, leading to occlusal disorders with discrepancy between centric relation and maximum intercuspation. To

avoid development of a TMD, reconstruction of harmonious occlusal relationship compared to the antagonist teeth during reconstruction procedure is highly recommended [50]. Condyle repositioning is difficult and requires a solid experience of stomatognathic system and occlusal consequence of this surgery. Nevertheless, even if surgeon is experimented, misplacement of the condyle is a common situation after a mandibular reconstruction [47,48]. Currently, surgeons can use virtual surgical planning to enhance the precise positions of anatomical structures (preserved native mandible, bone free flap, and TMJ) and optimize the jaw movements [19,51,52]. This element is even more important if the condyle is preserved or the patient has a residual dental occlusion.

Regarding the mandibular condyle, the following question remains: Should the surgeon preserve or sacrifice it? This is another key question to be answered when performing the surgical resection procedure. When a mandibular resection conserving the condyle unit is performed, condylar vascularization emanating from the superficial temporal artery, the maxillary arterial branches leading to the lateral pterygoïd muscle, and the deep posterior temporal artery are preserved [53]. Mandibular condylar preservation is then technically possible even if adjuvant treatments are planned. Since its conservation does not limit the oncological margins, it considerably improves the restoration of the mandibular function [48,54,55]. In children, the preservation of the condyle also facilitates mandibular growth, which to a better morphofunctional result [56–58]. Nevertheless, the surgeon often needs to resect the condyle to obtain satisfactory surgical margins in the treatment of malignant tumors. Preservation of the disc is then recommended when possible [59,60], especially in children where it could reduce impact on subsequent mandibular growth potential [61,62]. When this additional option is not possible, the

free extremity of the bone free flap is placed directly into the glenoïd fossa. Various techniques have been described to improve the congruence and remodeling of the free extremity of the bone free flap with equivalent results [54,59,61].

On the other hand, condylar status is not the only functional factor and imbalances of the remaining masticatory muscles after mandibular reconstruction seem to be another element to consider in TMD development process [63]. When a mandibular ramus resection has been performed, mandibular reconstruction is indeed associated with a greater risk of articular head dislocation, leading to TMD.

Mechanical paradigm does not stop with reconstructing the shape of the mandible, and in particular optimally repositioning the condyle unit, but also in restoration of vertical dimension of the jaws. Restoration of the oral cavity before adjuvant treatments and surgical excision of the malignant tumor are two situations in which a decrease in the vertical dimension of occlusion exists. The change of the resting position due to this reduction of vertical dimension of occlusion by removing teeth is considered to be a predisposing factor for TMD [64]. The harmonious function of the stomatognathic system indeed requires a suitable support from the natural dentition and the ridge areas or from the adequate designed prostheses [42]. To prevent muscle spasms and to restore correct muscular coordination, practitioners must fabric well-fitting dentures [64]. Masticatory performance and swallowing threshold performance are improved with prosthodontic rehabilitation [65,66]. Nevertheless, oral rehabilitation with dental prostheses is often difficult given the new anatomy of the mouth after mandibular reconstruction. Oral rehabilitation with dental osseointegrated implants solves some difficulties in this context [67]. Prosthetic choice is then fundamental, including a sealed or screwed bridge, resin-bonded bridge, tooled bar, implant borne denture, or implant stabilized dentures. Dental

implants may be used even in situations involving an unfavorable crown-to-root ratio and implant position by using milled bar and over denture.

*Radiation-induced changes of the stomatognathic system:*

Radiation-induced temporomandibular disorders as well as radiation-induced mouth-opening limitations have been frequently reported in postradiotherapy head and neck cancer patients. Both conditions are closely interlinked; Radiation - induced mouth-opening limitations can be due to different pathophysiological pathways, including manifestations of TMD such as internal disorders of the TMJ [68]. The best example of these situations is nasopharyngeal carcinoma, given the close proximity of the TMJ and masticatory muscles to the nasopharynx and the importance of delivered doses to these anatomical structures during radiotherapy [69–74]. Nevertheless, both situations can be encountered in all head and neck cancers, and therefore in oral cancer affecting the mandible, due to the pivotal role of radiotherapy in the treatment of patients with head and neck cancer [75]. Although mechanisms of both radiation-induced changes can be different, some aspects of these complications appear to be similar. Radiotherapy induces radiation fibrosis of head and neck tissues, and a decrease in vascularity along with denervation atrophy of masticatory muscles as well as injuries to the mandible and the TMJ [68,75]. It infers fibrotic changes with contracture in mastication structures, including the masseter and pterygoïd muscles, damage to their neural innervation and temporomandibular joint degeneration leading to limited mouth opening and pain-related symptoms included in TMD. Induced mandibular hypomobility due to radiation-induced fibrosis, potentially accentuate by other mechanisms such as intraoral surgical scar, will results in both muscle and TMJ degeneration. Indeed, muscle immobility induces

muscle atrophy [42]. Similarly, joint, which is immobilized quickly begins to show degenerative changes, including thickening of synovial fluid and thinning of cartilage [76]. The direct effect of radiation on muscle results in fibrosis and contracture with a gradual onset noted at about 9 weeks after treatment is completed [71,77]. There are a significant correlation between the absorbed dose to the mastication structures and opening of the mouth. Levels in excess of 60 Gy are more likely to cause trismus, and the dose of radiation delivered to medial pterygoïd muscles increased seem to be a key factor [78–80]. The probability of developing trismus is reported to increase 24% for every 10 Gy of additional radiation delivered to the medial pterygoïd muscles [79]. Intensity-modulated radiation therapy (IMRT) permits to decrease these results [74,80]. In the same way that Axis II elements impair the quality of life in head and neck cancer patients, there is a significant impact of trismus on the quality of life of these patients [72,81]. Patients with nasopharyngeal cancer reported the highest morbidity on the head and neck module (dry mouth, sticky saliva, trismus, problems with teeth, trouble eating). It may be explained by the location of the target volume, which included the bilateral temporo-mandibular joints [72]. This increases the role of radiotherapy in development of TMD, by accentuating the biopsychosocial mechanism.

There are several management options for trismus, including physiotherapy, pharmaceuticals, microcurrent therapy, oxygen therapy and coronoidectomy or forced mouth opening [68,75]. Its management is gradual and starts with the least invasive techniques. Exercise therapy stays the mainstay of the treatment of trismus, although its effectiveness of exercise therapy is limited. Exercising should start as soon as possible after surgery or during radiotherapy. Several mechanical methods have been advocated such as the use of finger stretching, tongue depressors or

spring appliances [82–85]. Jaw opening devices such as Therabite® is classically used to treat the mouth opening limitation as well as acute myogenic temporomandibular disorders [86]. Recent noninvasive options may be used in the management of both radiation-induced myospasm. Botulinum toxin A (BTxA) was suggested for pain control in a few cases [87–94]. However, such an injection to the TMJ region was only effective in alleviating radiation-induced pain due to radiation fibrosis syndrome, and a subsequent injection was needed to relieve recurrent masseter muscle pain. In addition, no significant improvement regarding the severity of trismus was demonstrated [92]. This therapeutic can also be used in a low concentration in chronic neuropathic pain of the neck and shoulder after neck dissection [88,95]. Moreover, BTxA improves the quality of life of patients with TMD [96] and in particular in cancer patients suffering from pain in the area of surgery and radiation [87,91]. Therefore, it seems to be an effective treatment of TMD in head and neck cancer, by relaxing the masticatory muscle, controlling the pain-related symptoms, and improving all elements included in axis II, such as quality of life and pain-related disability. Injections of platelet-rich plasma administered into the TMJ could represent another alternative in the management of TMD in the oncologic context. This therapeutic, used in TMJ osteoarthritis in general population [97], increases joint inflammation and then enhances the blood supply in rabbits, which results in the onset of regeneration of the TMJ after radiotherapy [98]. This could be an effective treatment in the management of late term musculoskeletal complications of radiotherapy in patients with head and neck cancer.

***Conclusion:***

Considering main specific mechanisms of TMD in the context of oral oncology is essential to enhance the mandibular function and optimize the quality of life of these patients. The precision of mandibular reconstruction and the interest of virtual surgical planning, conservation of the condyle, oral rehabilitation with dental osseointegrated implants to correct vertical dimension, or use of specific injections (Botulinum toxin or plasma-rich platelet) in masticatory muscles or temporomandibular joints are examples of the many ways to accomplish this. Distress prevention by using psychological interventions focused on relaxation, cognition, or behavior is another element.

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All authors have viewed and agreed to the submission.

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## Figures:

Figure 1. Management of the specific mechanisms of temporomandibular disorders in patients with head and neck cancers are represented: precision of mandibular reconstruction and interest of virtual surgical planning, conservation of the condyle, oral rehabilitation with dental osseointegrated implants to correct vertical dimension, or use of specific injections (Botulinum toxin or plasma-rich platelet) in masticatory muscles or temporomandibular joints. Distress prevention by using psychological interventions focused on relaxation, cognition, or behavior is another element.

